



Regulation of TCA Cycle & inhibitors

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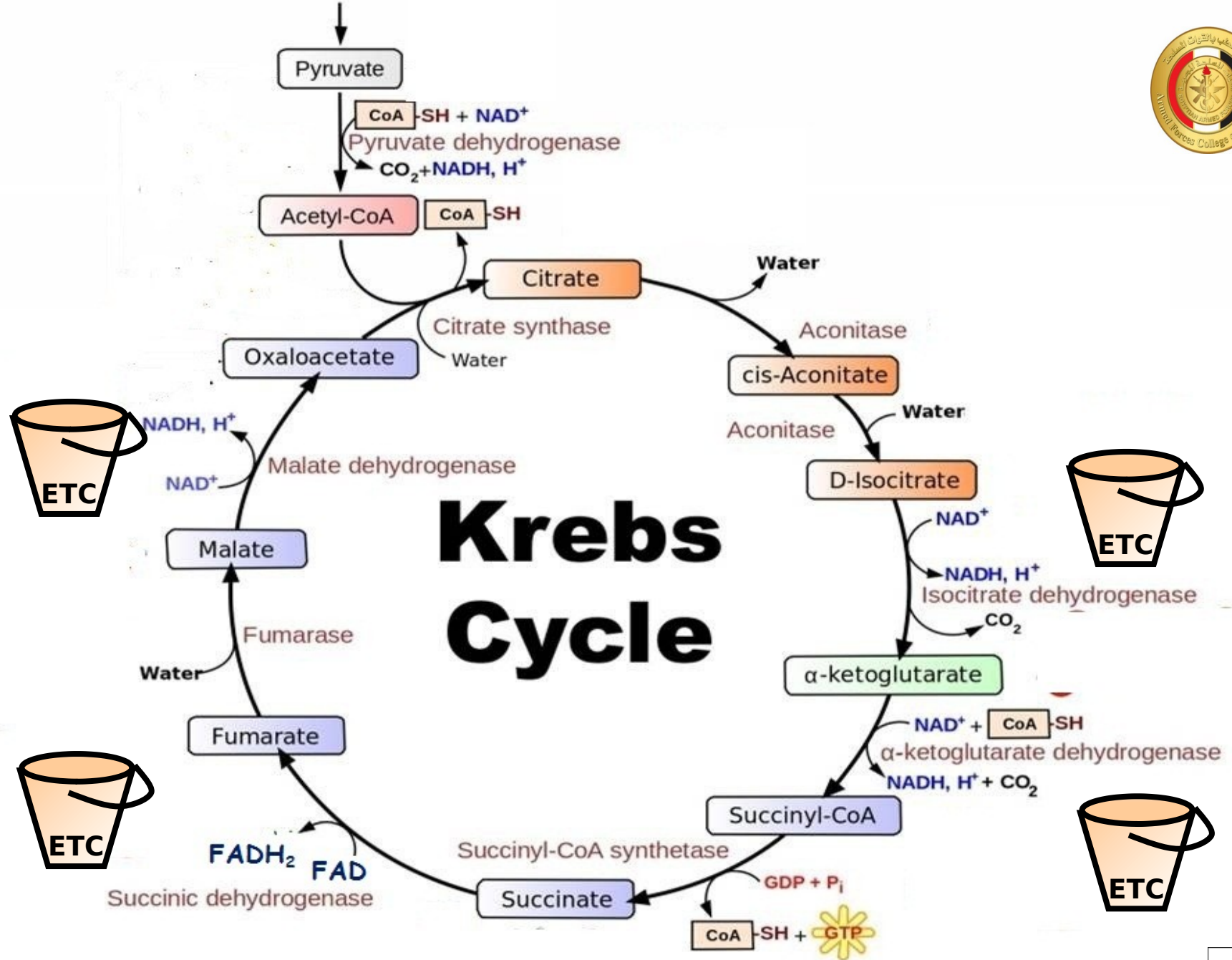
ILOs



By the end of this lecture, students are expected to

- 1. Explain anaploretic reactions of TCA cycle**
- 2. Outline the regulatory mechanisms of Krebs cycle**
- 3. Discuss the role of vitamins in TCA cycle**
- 4. Explain mechanism of action of inhibitors of TCA cycle**



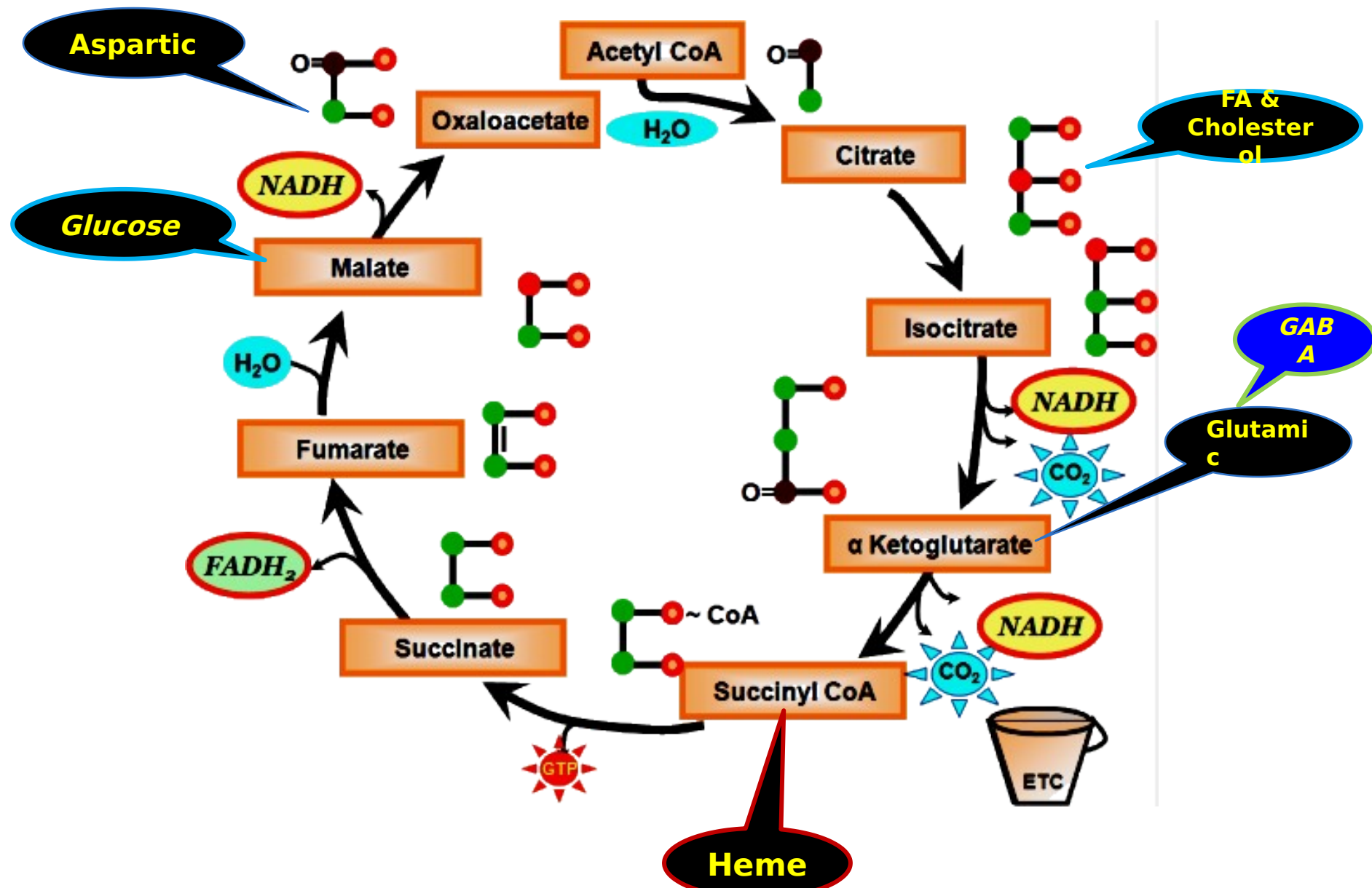




TCA cycle

in TCA the **2 carbons of acetyl CoA**
are
oxidized and released in the form
of **CO₂**, with concomitant
formation of

Efflux Of TCA Cycle Intermediates“Divergent ”



Anaploretic Reactions which replenish intermediates of TCA Cycle??

= Substrates Of TCA Cycle

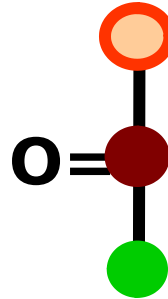
Since many intermediates of TCA cycle can be used for biosynthesis of some important derivatives so you need to replenish the intermediates of TCA cycle by reactions which are called anaploretic reactions

Anaplerotic Reactions

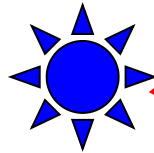
= Substrates Of TCA Cycle

Pyruvate Carboxylase

Pyruvate



1. Form Pyruvate Carboxylation

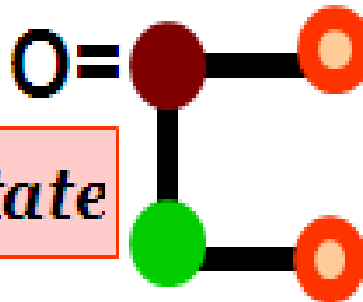


HCO_3^-

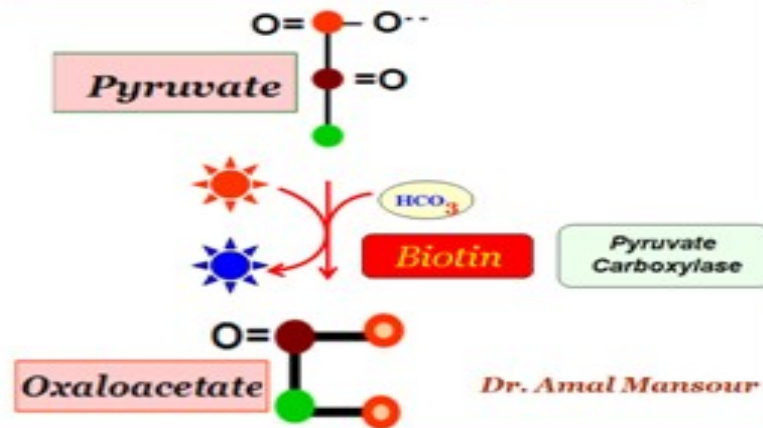
Biotin

*Pyruvate
Carboxylase*

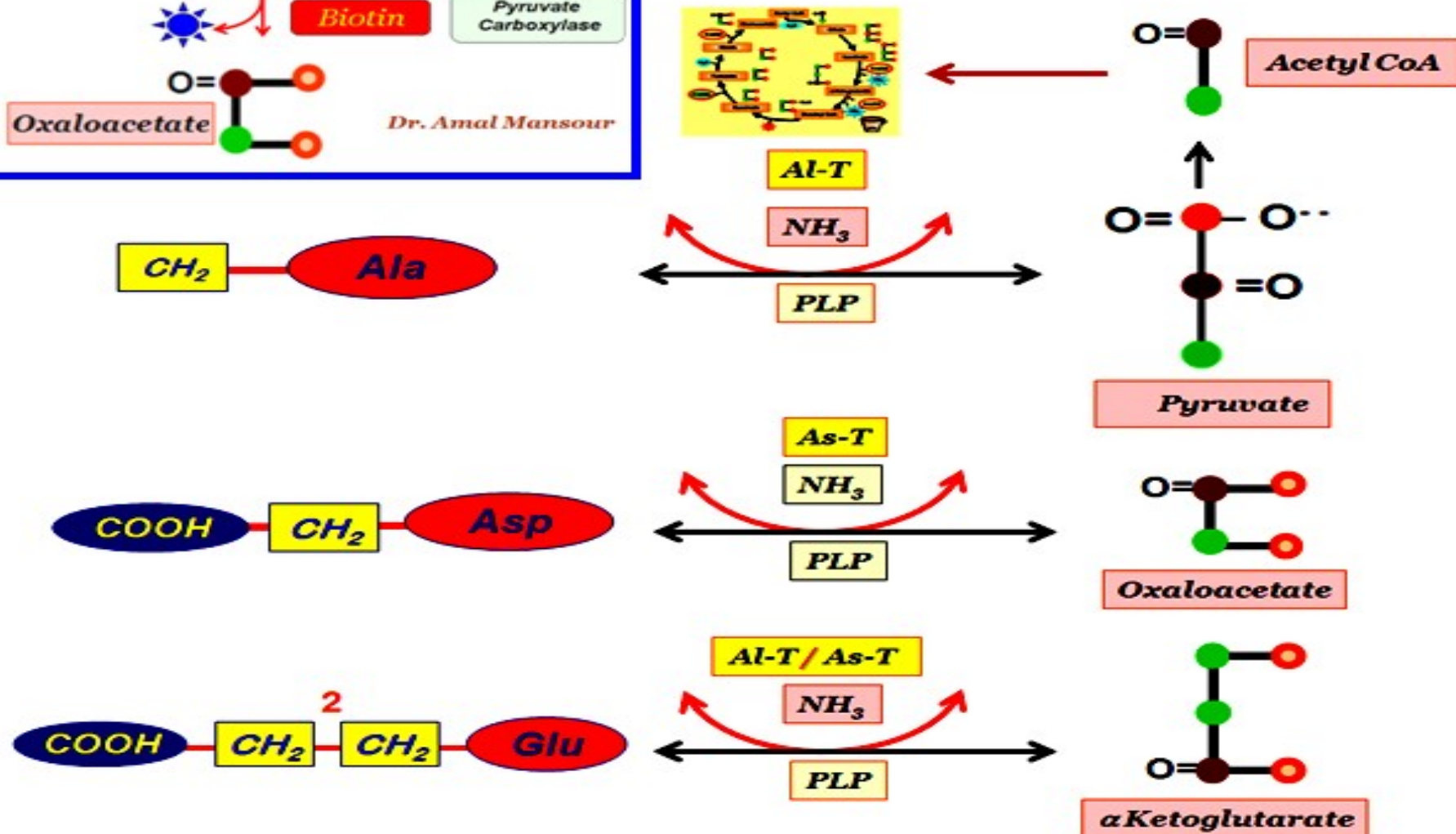
Oxaloacetate



Pyruvate Carboxylase



2. From Transamination of Non Essential a.a



Anaploretic Reactions are those that reestablishing intermediates in TCA cycle, which of the following enzyme catalyze anaploretic Reactions?

- a. α Ketoglutarate dehydrogenase**
- b. Pyruvate kinase**
- c. Malate dehydrogenase**
- d. Pyruvate carboxylase**
- e. Succinyl-CoA thiokinase**



**Deficiency of Any of
The Enzymes of The
TCA Has Not Been
Reported !!!**

**As it is incompatible with
life.**

Regulation of TCA cycle

(Short term)

1. Coarse Regulation (Substrate availability)

- 1. Low Energy State** (elevated ADP & NAD⁺)
- 2. Availability of O₂**
- 3. Acetyl CoA & oxaloacetate**



Accelerates the Rate of Reactions !!

2. Fine Regulation (Allosteric Control)

KEY REGULATORY ENZYMES

1. Citrate synthase

*** Allosteric inhibitors:** NADH, citrate & succinyl CoA

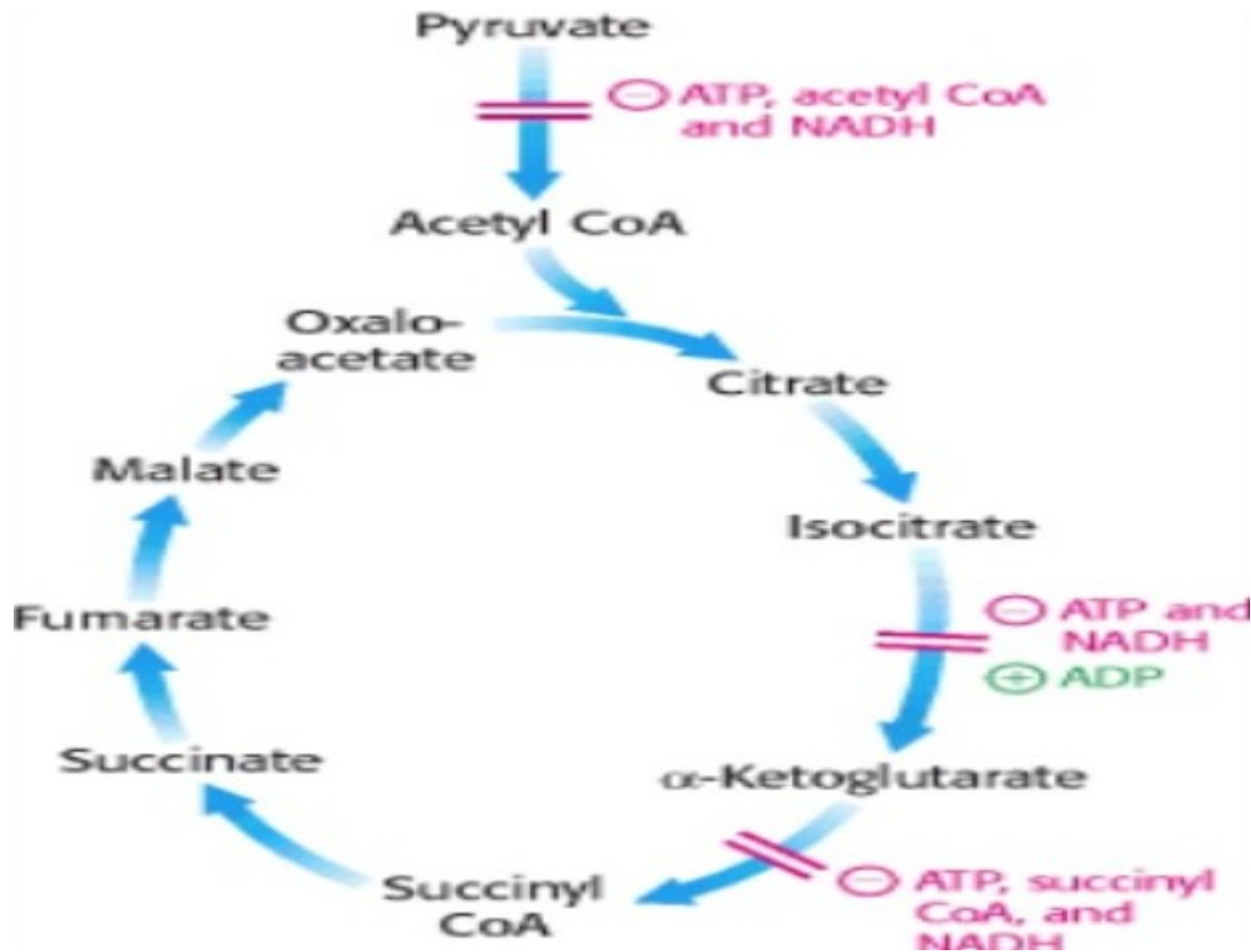
2. Isocitrate dehydrogenase

- **Allosteric inhibitors:** NADH and ATP
- **Allosteric activators:** ADP and calcium

3. α - ketoglutarate dehydrogenase

- **Allosteric inhibitors:** NADH, ATP, GTP & succinyl CoA
- **Allosteric activators:** NAD⁺, ADP and Calcium

Allosteric Regulation of TCA cycle



How is the **rate of the TCA cycle** linked to **muscle contraction** and the utilization of **ATP**?



When Ca^{++} increases in muscle cells, muscle contracts and all of the following will happen:

Isocitrate.D, α - ketoglutarate.D & PDH.

Allosterically Activated

by $\uparrow\uparrow$ in Ca^{++} & by $\uparrow\uparrow$ in ADP , NAD, & FAD.

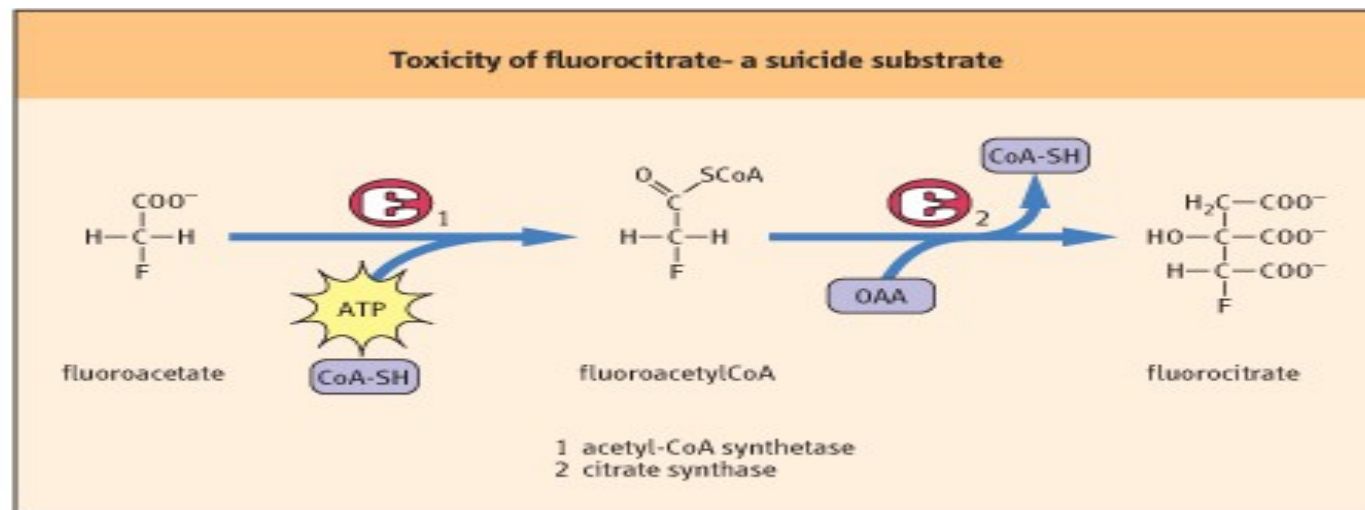
Vitamins required for reactions of the TCA cycle

1. **Niacin** for the synthesis of NAD which is used in the isocitrate dehydrogenase, α -ketoglutarate dehydrogenase, and malate dehydrogenase reactions.
2. **Riboflavin** for the synthesis of FAD, which is the cofactor for succinate dehydrogenase and α -ketoglutarate dehydrogenase.
3. **lipoic acid** cofactor for α -Ketoglutarate dehydrogenase.
4. **Thiamine** is used for the synthesis of thiamine pyrophosphate; a cofactor for α -Ketoglutarate dehydrogenase.
5. **Pantothenate** for CoASH, a cofactor for α -

Inhibitors of TCA cycle??

1. Fluoroacetate (rat poison)

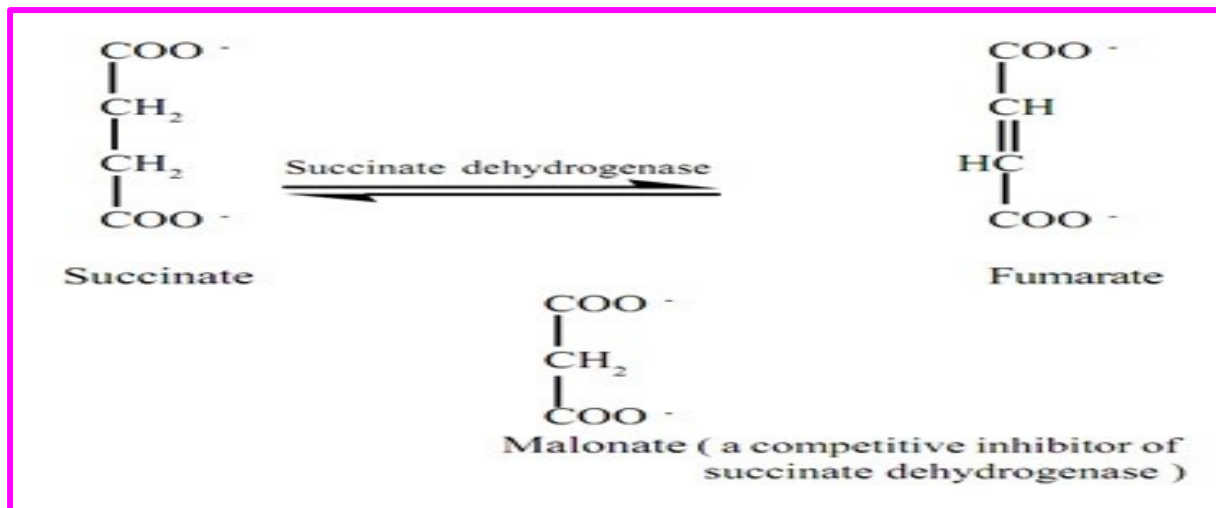
- Give fluoroacetylCoA that condense with oxaloacetate to form fluorocitrate which inhibits aconitase enzyme



Inhibitors of TCA cycle; con..

2. Malonate

- ❑ Similar to succinate
- ❑ *Inhibits Succinate dehydrogenase (competitive inhibition)*



Inhibitors of TCA cycle; con..

3. Arsenite poisoning:

- **Source:** Drinking water contaminated with arsenic
- **Mechanism:** inhibits enzymes and cofactors that contain adjacent free sulfhydryl groups (such as **lipoic acid**), and will interfere with TCA cycle reactions (**pyruvate dehydrogenase and a-ketoglutarate dehydrogenase**, it is fatal because it inhibits energy production).
- **Symptoms:** vomiting, abdominal pain, encephalopathy, and watery diarrhea that contains blood.
- **Diagnostic method:** Urine, blood, or hair testing

Arsenic's Effects on the Human Body

Nervous System

Impaired intellectual function
Impaired motor function
Neuropathy

Cardiovascular System

Coronary heart disease
Hypertension
Heart attack

Renal System

Kidney cancer
Bladder cancer

Skin

Skin lesions
Skin cancer

Endocrine System

Diabetes
Impaired glucose tolerance in pregnant women

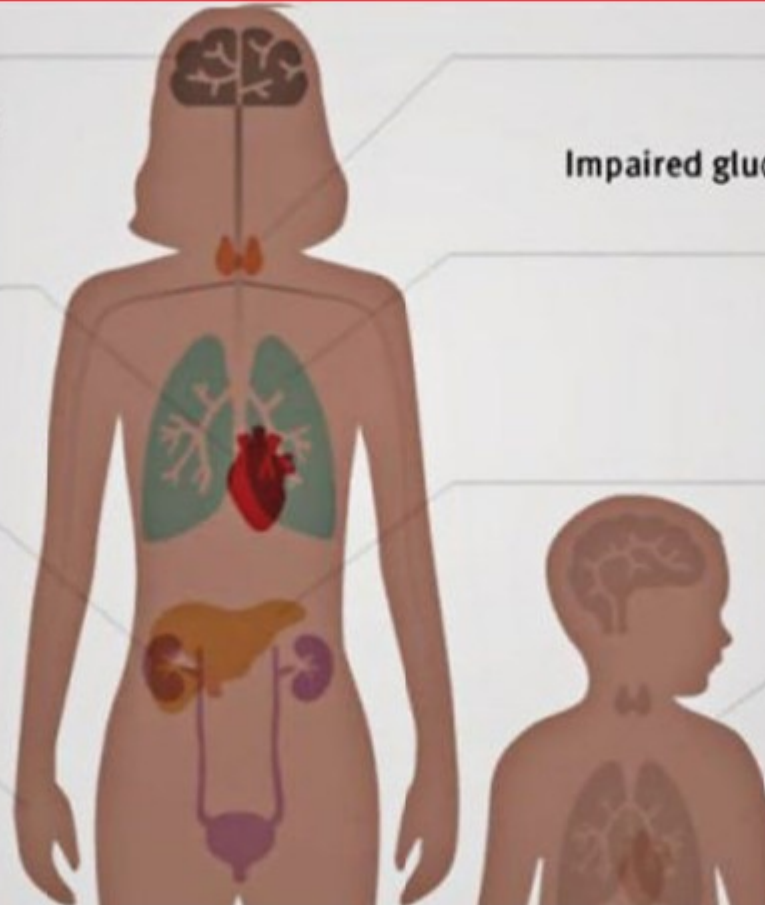
Respiratory System

Pulmonary tuberculosis
Bronchiectasis
Lung cancer

Liver cancer

Developmental Process

Increased cancer risk as adults
Increased infant mortality
Neurological impairment
Reduced birth weight



Test your self

1. _____ is the first compound that is oxidized in the citric acid cycle.
2. _____ is an enzyme that catalyzes a substrate-level phosphorylation.
3. The citric acid cycle intermediate _____ is found at the beginning and at the end of the citric acid cycle.

1. acetyl CoA
2. Succinyl CoA
thiokinase
3. Oxaloacetate



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- b. Pyruvate kinase**
- c. Malate dehydrogenase**
- d. Pyruvate carboxylase**
- e. Succinyl-CoA thiokinase**





Take Home Message

- The TCA cycle is regulated by the **cell's need for energy** in the form of ATP molecules.
- Cofactors, many of which are minerals or compounds produced from vitamins, aid the enzymes of TCA cycle.
- Inhibitors of TCA cycle is fatal because it inhibits energy production

SUGGESTED TEXTBOOKS



- ✕ "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier
- ✕ "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.
- ✕ Fundamentals of Clinical Chemistry (Tietz) Sixth
- ✕ "Textbook of Biochemistry with Clinical Correlations" by T.M.Devlin
- ✕ www.namrata.co- ***Biochemistry for medics***

Thank you!

